UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte LYNN E. SPITLER and ANTHONY E. MAIDA, III

Appeal No. 2004-1185
Application No. 09/300,978

HEARD: November 16, 2004

Before WINTERS, WILLIAM F. SMITH, and ADAMS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's refusal to allow claims 13, 15, 16, and 18-24. The examiner stated in a communication mailed February 23, 2004, that claims 13, 15, 18, and 20-24 have been examined to the extent they read upon the elected species, human prostate-specific membrane antigen (PSMA) and that claims 16 and 19 were inadvertently rejected since they are directed to the nonelected species, prostatic acid phosphatase (PAP). The examiner stated that claims 16 and 19 were withdrawn from consideration. Id. Thus, claims 13, 15, 18, and 20-24 are before us for consideration with claim 13 having been examined only with regard to the elected species PSMA.

Claim 13 reads as follows:

13. A method to elicit an antitumor immune response to prostate tumors in a subject, which methods comprises

administering to said subject at least one active ingredient formulated for administration to said subject,

wherein said active ingredient comprises or expresses at least one antigen over-represented in the prostate gland,

wherein said antigen is human prostate-specific membrane antigen (PSMA); or

prostatic acid phosphatase (PAP); or mixtures of the foregoing; or

wherein said active ingredient comprises said at least one antigen or nucleic acid that generates said antigen or antigens in situ.

The evidence relied upon by the examiner is:

Horoszewicz	5,162,504	Nov. 10, 1992
Grauer et al. (Grauer)	5,250,297	Oct. 5, 1993
Linnenbach (Linnenbach '254)	5,185,254	Feb. 9, 1993
Israeli et al. (Israeli)	5,538,866	Jul. 23, 1996
Linnenbach et al. (Linnenbach '002)	5,668,002	Sep. 16, 1997
Spitler	5,738,867	Apr. 14, 1998

Varki et al. (Varki), "Antigens Associated with a Human Lung Adenocarcin ma D Fined by Monoclonal Antibodies," Cancer Research, Vol. 44, pp. 681-687 (1984)

McCarley et al. (McCarley), "Diagnostic and Therapeutic Utility of Monoclonal Antibodies in Urologic Oncology," Seminars in Surgical Oncology, Vol. 5, pp. 293-301 (1989)

Paul, ed., "Differentiation Antigens and Other Tumor-Associated Antigens," Fundamental Immunology, Second Edition, p. 931, col. 1, paragraph 1 (Raven Press, New York 1989)

Sela et al. (Sela), "Colon Carcinoma-Associated Glycoproteins Recognized by Monoclonal Antibodies CO-029 and GA22-2," Hybridoma, Vol. 8, No. 4, pp. 481-491 (1989)

Andriole et al. (Andriole), "The Diagnosis and Treatment of Prostate Cancer," Ann. Rev. Med., Vol. 42, pp. 9-15 (1991)

Kuby, Immunology, Second Edition, p. 590, col. 2, p. 613 (W.H. Freeman and Company, New York 1994)

Cruse et al. (Cruse), Illustrated Dictionary of Immunology, p. 302 (CRC Press, Boca Ration 1995)

Claims 13, 15, 18, and 20-24 stand rejected under 35 U.S.C. § 103(a). The examiner relies upon Spitler, Israeli, Horoszewicz, Andriole, McCarley, Cruse, Kuby, Paul, Grauer, Varki, Linnenbach '254, Linnenbach '002, Sela, and "art acknowledged methods of delivering antigens of interest to stimulate antitumor responses, as disclosed on page 10-19 of the instant specification" as evidence of obviousness. Examiner's Answer, page 5. We affirm.

Background

Human prostate specific membrane antigen (PSMA) is an integral membrane protein. Specification, page 9. Appellants state:

> The PSMA (molecular weight 100,000) ... has representation on both benign and neoplastic prostate cells with more intense staining seen with malignant cells. Metastases of prostate cancer also have representation of the antigen. This antigen, therefore, is an [sic] appealing as a vaccine candidate for the same reasons as those described for PSA [prostate specific antigen]. Moreover, PSMA is an integral membrane protein rather a secreted protein as is PSA, and, therefore, may be an even more appropriate vaccine component.

Id.

As seen from claim 13 on appeal, PSMA is used in the claimed invention as an active ingredient that is administered to a subject in order to elicit an antitumor immune response to prostate tumors. As set forth in claim 13, the active ingredient used in the method, i.e., PSMA, must be "over-represented in the prostate gland." Appellants define "over-represented" as meaning "the concentration of [the] antigen in prostate is sufficiently higher than its concentration in any other tissue such that the prostate can effectively be targeted by the immune response raised against [the] antigen with relative sparing of other organs or tissues." Specification, page 5.

Discussion

1. Separate Argument of Claims.

Appellants state at page 4 of the Appeal Brief that "all claims may be considered together for purposes of the rejection under 35 U.S.C. § 103." Since claim 13 is the only independent claim subject to this appeal, we shall limit our considerations of the issues in this appeal as they pertain to claim 13. See the then-existing provisions of 37 CFR § 1.192(c)(7).

2. Preliminary Issue.

Appellants question in the paragraph bridging pages 11-12 of the Appeal Brief whether Kuby or Cruse is properly prior art to the claimed invention. Appellants state that the effective filing date of the claims on appeal is August 11, 1993, and the publication dates for Kuby and Cruse are 1994 and 1995, respectively.

The examiner appears to acknowledge the argument at page 28 of the Examiner's Answer, stating "Appellant [sic] argues that Kuby and Cruse

are [not?] properly prior art to the claimed invention because the instant priority is August 11, 1993." However, the examiner does not respond directly to the issue of whether Kuby or Cruse is available as evidence of obviousness in this case. Rather, the examiner goes on to discuss why Kuby and Cruse are relied upon in maintaining the rejection. Examiner's Answer, page 29.

In considering this issue, we note the examiner has not disputed that the effective filing date of the claims on appeal is August 11, 1993. Nor has the examiner disputed that the publication dates of Kuby and Cruse are after this effective filing date. Since we have no effective response from the examiner to this argument, we shall consider the obviousness issue raised in this appeal on the basis that Kuby and Cruse are not available as prior art.

3. Obviousness of Claim 13.

As discussed above, claim 13 is directed to a method to elicit an antitumor immune response to prostate tumors in a subject. To this end, PSMA is administered as an active ingredient to the subject. Claim 13 also states that PSMA is over-represented in the prostate gland.

Spitler[1] describes antitumor vaccine compositions and methods for treating tumors. Specifically, the method described by Spitler employs liposome compositions that encapsulate or are conjugated to tumor associated antigens (TAAs) or anti-idiotypic monoclonal antibodies (anti-ids) to TAAs. Spitler, column 2, lines 16-19.

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[1] Spitler is named as a co-inventor of the present application.

Spitler does not define TAA. However, Spitler discusses two specific TAAs, CO-029 and GA733-2 are follows:

> Of particular interest are liposome compositions encapsulating the TAAs CO-029, associated with tumors of the gastrointestinal tract, colorectum, and pancreas and GA733-2, associated with tumors of the gastrointestinal tract, prostate, cervix, ovary, bladder, lung, breast, colorectum, and pancreas.

Id., column 2, lines 21-26.

While TAA GA733-2 is associated with a number of organs including the prostate, the examiner has not asserted that GA733-2 is an antigen that is over-represented in the prostate gland as is PSMA. Rather, the examiner's position is that PSMA would be considered a TAA by a person of ordinary skill in the art at the time of the present invention and thus, that hypothetical person would have found it obvious to use PSMA in the antitumor method described in Spitler.

Of the three documents relied upon by the examiner as defining TAA, only Paul is available as prior art. Paul discusses TAAs as follows:

> Some antigens expressed on tumor cells are also expressed on normal cells during at least some stage of differentiation, and many of these antigens can be considered as differentiation markers. The extent to which these differentiation antigens are expressed by normal cells and issues can vary from widespread expression to extreme restriction by a small clone of normal cells. Furthermore, the time during development when these markers are expressed on normal cells can vary considerably. Since none of these antigens is tumor specific, they are commonly referred to as 'tumor-associated' antigens. These antigens represent a very diverse group of glycoproteins and glycolipids.

Paul, page 931, column 1, second paragraph.

Thus, Paul distinguishes between "tumor-associated" antigens and antigens that are "tumor specific." A TAA is an antigen that is expressed on tumor cells and normal cells during at least some stage of differentiation.

PSMA meets the definition of TAA set forth in Paul and is discussed in both Horoszewicz and Israeli. Horoszewicz describes monoclonal antibodies that:

> demonstrate a narrow spectrum of organ-specific reactivity with non-soluble, membrane associated antigenic determinants (epitopes) present on normal neoplastic and malignant human prostatic epithelium. The monoclonal antibodies do not react specifically with non-prostatic tumors and other tissues. The monoclonal antibodies stain malignant prostatic cells intensely and non-malignant prostatic epithelium weakly.

Horoszewicz, column 6, lines 50-58. One of the monoclonal antibodies described by Horoszewicz is designated as 7E11-C5. Id., column 17, line 9. While Horoszewicz does not state that the antigen which 7E11-C5 binds is PSMA, Israeli closes the circle in this regard. See Israeli, column 2, lines 1-57. We find no dispute on the record that both Horoszewicz and Israeli describe PSMA.

PSMA is over-represented in the prostate gland and meets the definition of TAA set forth in Paul. The former is seen in that Horoszewicz states that the monoclonal antibodies of the reference do not react specifically with non-prostatic tumors and other tissues. Id., column 6, lines 54-56. The latter since Horoszewicz states that the monoclonal antibodies of that reference stain malignant prostatic cells intensely and non-malignant prostatic epithelium weakly. Id., column 6, lines 56-58. Thus, the antigen to which 7E11-C5 binds, PSMA, is not tumor specific since it is present on non-tumorous prostatic tissue. Thus, according to Paul's definition, PSMA is a TAA.

Having determined that PSMA is a TAA that is over-represented in the prostate gland, the question becomes would it have been obvious to a person of ordinary skill in the art at the time of the present invention to use PSMA in the anti-tumor vaccine described by Spitler? We answer this question in the affirmative.

Spitler is broadly directed to the use of TAAs as tumor vaccines. Importantly, Spitler is interested in combating prostate tumors since one of the specific TAAs discussed, GA733-2, is stated to be associated with prostate tumors. In our view, the question now becomes would a person of ordinary skill in the art use PSMA as the TAA in a vaccine according to Spitler with the requisite reasonable expectation of success? In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). We find Horoszewicz provides evidence that supports this conclusion.

As mentioned previously, Spitler states that either TAAs or anti-ids to TAAs are effective in the vaccine compositions of that invention. Horoszewicz states that administration of 7E11-C5 expectedly produces anti-ids to PSMA which may result in the modification of the host's anti-tumor immune response. Horoszewicz, column 12, lines 4-29. From these facts, it is reasonable to conclude that a vaccine based upon PSMA itself instead of anti-ids to PSMA would be effective against prostatic tumors.

Thus, we find no error in the examiner's conclusion that the subject matter of claim 13 on appeal as a whole would have been obvious to a person of ordinary skill in the art at the time of the present invention.

Appellants first argue that Spitler does not teach or suggest the use of organ-specific antigens such as PSMA to elicit an antitumor response in a subject. Appeal Brief, pages 9-10. We agree, as did the examiner, that the two specific antigens

discussed in Spitler, CO-029 and GA733-2 are not antigens over represented in the prostate gland as required by claim 13 on appeal. However, appellants' argument overlooks the broader disclosure in Spitler of using TAAs in general.

Appellants recognize that Horoszewicz does describe an active immunotherapy protocol as required by claim 13 on appeal but state that the protocol of Horoszewicz only employs anti-ids which appellants believe provide a "fundamentally different therapy" than use of an antigen per se. Id., page 11. In making this argument, appellants do not further explain their argument in regard to "fundamentally different therapy." Nor do appellants recognize that Spitler itself states that either therapy, i.e., use of an antigen or an anti-id, will work in the tumor vaccines of that reference. While the underlying mechanisms by which an antigen and anti-id trigger an anti-immune response in a host will differ, Spitler states that the end result will be the same, an effective immunotreatment of a tumor.

Appellants also argue that Spitler teaches away from the method required by claim 13 in that Spitler teaches that the compositions of that invention are useful in treating a variety of cancers. Appeal Brief, page 13. Appellants further argue that a person of skill in this art would understand that the administration of a vaccine that elicits an immune response to an antigen on normal tissues would result in autoimmunities specific for that tissue, a potentially fatal side effect. Id. In our view, this argument again loses sight of the broader description in Spitler of using TAAs in general and the specific disclosure of Horoszewicz and Israeli in regard to PSMA. While the two specific TAAs discussed in Spitler may very well be useful in treating a variety of tumors, it is equally clear that immunotherapy of prostatic cancer based upon

PSMA would be specific to prostatic tissue whether normal or malignant as discussed in Horoszewicz and Israeli. Furthermore, since PSMA is specific to the prostate gland, its use in an antitumor vaccine would not be expected to harm other tissues. Destruction of the prostate gland would not be considered a potentially fatal side effect.

Turning to the Reply Brief, we find appellants argue that the TAAs used by Spitler do not encompass PSMA, stating that "PSMA is an antigen that is overexpressed on normal prostate tissue as well as prostate tumor" and that one of ordinary skill in the art would not view PSMA as a desirable target. Reply Brief, pages 3-5. Appellants do not cite to the record in making these arguments.

In reponse, we again reference the disclosure of Horoszewicz that the monoclonal antibodies of that reference "stain malignant prostatic cells intensely and non-malignant prostatic epithelium weakly. Horoszewicz, column 6, lines 56-58. Thus, this argument is not supported on the record. Contrary to appellants arguments, a joint reading of Spitler, Horoszewicz and Israeli shows that PSMA would be a desirable target.

Appellants next argue that the combination of references relied upon by the examiner is improper. Reply Brief, pages 5-8. We disagree. In making this argument appellants acknowledge that Horoszewicz describes active immunotherapy using prostate-specific anti-ids but characterize this disclosure as "limited." Id., page 6. In making this argument appellants do not come to grips with the fact that Spitler itself states that use of an antigen or anti-ids to the antigen will be useful in those vaccine composition.

The same can be said in regard to the argument set forth on page 8 of the Reply Brief as to the differences between anti-id therapy and antigen-based therapy. The two forms of therapy may act through different mechanisms but the end result according to Spitler will be the same.

Finally, appellants argue on pages 8-10 of the Reply Brief that the specific antigens described by Spitler are associated with a number of malignant cells that differ histologically and genetically. Be that as it may, Spitler broadly suggests the use of TAAs in the vaccine of that reference and PSMA is reasonably classified as a TAA.

The decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Sherman D. Winters
Administrative Patent Judge

William F. Smith
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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